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Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years☆

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ABSTRACT

In 1999, the Global Advisory Committee on Vaccine Safety (GACVS) was established by the World Health Organization (WHO) to provide independent scientific advice on issues relating to the safety of vaccines and immunization. Fifteen years onward, we conducted a multi-faceted review to evaluate the impact, reach and challenges facing GACVS, including the role GACVS plays in informing global, regional and WHO member state vaccine policy. The methods included measures of organizational structure, citation impact, themes approached, and a discussion by previous and current members to evaluate past, present and future challenges. Given the increasing range of data sources and the deployment of many new vaccines, the Committee is facing the complex task of identifying the best available evidence for recommendations on vaccine safety. To help meet the increased demand for public transparency in decision making, GACVS-structured methodology for evidence-based decisions is evolving. GACVS also promotes best practices and capacity building for timely and accurate risk assessment; risk communications; outreach to help countries maintain and, if needed, rebuild public trust in vaccines; and advocacy for bridging the major gaps in vaccine safety capacity globally.

1. Introduction

Since vaccines are usually administered to healthy individuals to prevent their target vaccine-preventable diseases (VPD), they are typically held to a higher standard of safety than medicinal products used to treat ill patients. To identify common and less common (but not rare) problems at the preapproval stage, vaccines undergo extensive safety and efficacy studies needed to fulfill stringent regulatory licensure requirements [1,2]. Due to the limited size and scope of pre-licensure safety studies, however, post licensure monitoring and evaluation is needed and increasingly performed to identify rare safety concerns. For two centuries, vaccines have demonstrated their public health value in preventing and controlling infectious diseases that previously injured or killed millions of individuals globally each year. However, these successes in controlling and in some cases eliminating their target VPD have paradoxically resulted in increased concerns about the safety of vaccines in recent decades [3]. Occasionally, rare serious adverse vaccine reactions occurring less frequent than one in 10,000 doses may become evident after a new vaccine is in widespread use in the

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general population [4–6]. But more commonly, as vaccine coverage reach high enough level to decrease the threat of VPDs, there is also a concomitant increase in coincidental adverse event following immunization (AEFI). Due to "*post hoc ergo propter hoc*", a common public misunderstandings about logic, these AEFIs may be falsely attributed as being caused by immunization. This misattribution seems particularly common for medical conditions whose etiology and pathophysiology are incompletely understood (e.g. autism, and multiple sclerosis). As information sharing via internet becomes all too easy, however, so is the propagation of such errors [7].

In the absence of adequate capacity to confirm or reject such AEFI's being caused by vaccination in a timely manner, loss of public confidence in a vaccine may occur (manifested as either hesitancy or refusal resulting in reduced coverage), with consequent return of outbreaks of VPDs [8,9]. Enhanced surveillance coupled with sound epidemiologic studies for vaccine safety from the local to the global levels helps provide the best evidence for decision making by parents, patients, providers, policy makers and society. This is a challenging capacity building process, especially in low and middle income countries (LMIC) where AEFI surveillance, investigation and management are often not well established. This process requires long-term commitment and significant resources to create the required safety monitoring infrastructure. The Global Advisory Committee on Vaccine Safety (GACVS) was established by the World Health Organization (WHO) in 1999 due to the growing need for independent review of the (often limited) available evidence and to provide recommendations on emerging vaccine safety issues globally, but especially for LMICs lacking such capacity [10–13]. This paper presents an analysis and review of the work and impact of GACVS over its 15 years of existence with suggestions for further improvements.

2. Methods

The review of GACVS's contributions and challenges was undertaken at the Center for Global Health, University of Colorado Denver, USA along with discussions by a panel of experts who were current or previous members of the GACVS. The WHO GACVS Secretariat provided support and assistance with access to archival documentation. The review encompassed: (a) an organizational evaluation of GACVS to define its composition, expertise, geographical representativeness; (b) an assessment of the GACVS's activities through a quantitative review of its reports, and an estimation of their impact on their global, regional and country target audiences; and finally, (c) a regulator evaluation survey. The GACVS composition, membership history, geography and professional backgrounds were obtained from a previous independent review of WHO immunization advisory committees and the list of current and past members available at the WHO website [14,15].

Given that direct assessment of GACVS's impact on the science of vaccine safety or on the shaping of local, regional and global vaccine policy was difficult, an indirect measure, the citation factor through Google Scholar Impact, was used. To undertake this, all GACVS meeting reports accessible on its website (from 1999 until 2014) as well as other GACVS and WHO publications in the scientific literature and related reports and guidelines were evaluated for thematic content, type of recommendation and impact generated in the published literature. The keywords "gacvs" and "Global Advisory Committee on Vaccine Safety" were used and the relevant publications ranking, number of references linked and their relevance to other scholarly literature was obtained. Whereas most academic databases and search engines allow users to select one factor (e.g. relevance, citation counts, or publication date) to rank results, Google Scholar grades them using a combined algorithm. For all topics reviewed by GACVS, the date of the Committee review was noted and the number of recommendations and conclusions per year recorded. For every GACVS conclusion, we classified the action as: (a) review of the evidence, (b) recommendation of a policy modification, or (c) request for additional research or evidence. The WHO vaccine position papers were also evaluated to determine if GACVS recommendations had been incorporated and cited as part of the review [16].

As there is no formal process to gauge the visibility and consumer use of GACVS recommendations beyond WHO, we designed a nine item qualitative survey. It was administered in a confidential manner to a convenience sample of drug regulatory experts from all six WHO regions who were attending a forum for drug regulation (International Conference of Drug Regulatory Authorities – ICDRA – August 27–29, 2014). Participants were asked about their knowledge of GACVS as well as the WHO's Weekly Epidemiological Record (WER), and the importance of GACVS recommendations in their regulatory work on vaccines.

Finally, to help identify the challenges and opportunities faced by GACVS, we held a discussion amongst previous and current members at the June 2014 GACVS meeting [17]. Presentations on past work of GACVS and results from the organizational and impact evaluation were used to stimulate discussion. These discussions were recorded, transcribed and themes related to contributions to the vision and future work of GACVS were noted.

3. Results

3.1. GACVS organizational assessment

GACVS has been an independent scientific advisory group to WHO, responsible for providing: (a) technical advice on vaccine safety; (b) assessment of risks related to vaccines in order to assist policy-makers in balancing benefits and risks as part of evidence-based policies; and (c) guidance on the development of vaccine safety systems, strategies and mechanisms to strengthen vaccine safety at the national and global levels [18].

GACVS is composed of experts from around the world in the fields of vaccine safety, vaccinology and allied sciences such as epidemiology, biostatistics, pharmacovigilance, biologic product regulation and clinical medical sciences. The committee's ~15 members are selected by an open application process organized by the WHO secretariat. Members serve on the Committee for three years with possible renewal for a second term. Over the past 15 years, GACVS has had 41 members from 20 different countries, representing all WHO regions, although 26 (63.4%) originate from high-income countries in Europe, North America and Australia as vaccine safety expertise is highly technical (Fig. 1).

GACVS members participate in bi-annual in-person meetings; they also work in topic specific sub-groups to develop statements (e.g. vaccines and HIV, vaccines in pregnancy, etc.). The Committee also meets as needed by teleconference in response to new or emerging issues. For example, in early 2010, academic investigators reported finding that one manufacturer's rotavirus vaccine contained DNA from porcine circovirus type 1 [19]. The committee met by teleconference on March 25, 2010, and posted a statement on line the following day [20].

The GACVS agenda is determined by its current and former members, together with the WHO secretariat (who incorporates the needs of the Strategic Advisory Group of Experts (SAGE), WHO's principal advisory group for vaccines and immunizations [21]). National immunization programs and WHO Regional Offices may also bring forward safety issues for consideration. Invited experts and observers may contribute in providing the Committee with up to date specific information but decisions or recommendations are,

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